REGIONAL BLOOD FLOW AND OXYGEN UPTAKE IN SEVERE SEPSIS

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Charles J. Wright

Department of Experimental Surgery M.Sc.

Measurements were made of cardiac output, blood flow in skeletal muscle, oxygen uptake, and femoral and total arteriovenous oxygen differences, before and after induction of a septic lesion in dogs. Half of the animals developed a hyperdynamic circulation in response to sepsis, and the rise in cardiac output was significantly correlated with an increase in muscle capillary blood flow, demonstrating that no pre-capillary arteriovenous shunts were present. The increased flow was also related to decreased arteriovenous oxygen extraction.

It was also demonstrated that after muscle exercise, in contrast to the findings after sepsis, the arteriovenous oxygen extraction was increased.

This study suggests that the sequence of events seen in hypovolemic or cardiac shock (where low tissue perfusion and tissue hypoxia cause secondary cellular damage) is reversed in septic shock; a primary cellular defect occurs, causing the hemodynamic disturbance as an attempted compensatory mechanism.

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Charles J. Wright

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Department of Experimental Surgery of the Royal Victoria Hospital and McGill University

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PREFACE

This project arose largely from the previous work of Drs. Lloyd D. MacLean, J.H. Duff and A.P.H. McLean who have made a special study of septic shock in recent years at this centre. I would like to express my warmest thanks to them for constant advice and encouragement during the project's execution.

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INTRODUCTION

It is well known that patients with severe sepsis often have a hyperdynamic circulation with raised cardiac output, lowered total peripheral resistance, and increased oxygen consumption. This hyperdynamic circulatory state may be maintained even when arterial hypotension develops and the oxygen consumption begins to fall. Several explanations are possible for this apparently paradoxical situation in which high or normal blood flow is associated with reduced oxygen uptake by the tissues. First, the blood flow is not available for tissue respiratory exchange if pre-capillary arteriovenous shunts are open, and a high cardiac output develops if the shunted volume of blood is sufficiently large. Secondly, the transport of oxygen from alveolar air to the cells throughout the body may be impaired. This could be due to changes in the lung, in the hemoglobin level, or in the factors which influence oxyhemoglobin dissociation. Thirdly, the cells' oxidative processes may be impaired, leading to reduced oxygen uptake even when there is normal or increased tissue perfusion by adequately oxygenated blood.

The question arises as to whether these patients with a hyperdynamic circulation in "septic shock", are really in shock, as this is often defined as a condition characterised by low

tissue perfusion. It is widely recognized, however, that while this definition is very appropriate in hypovolemic or cardiac shock, it does not fit the hemodynamic findings in many cases of septic shock. The diagnosis of "shock" is still appropriate for these patients as they exhibit the combination of arterial hypotension, metabolic acidosis, increasing blood lactate and oliguria.

This study was designed to investigate peripheral capillary hemodynamics in relation to peripheral oxygen extraction and total oxygen uptake, in severe sepsis and thereby to attempt an assessment of the relative importance of a primary peripheral cellular defect as opposed to one of hemodynamics in the pathogenesis of septic shock.

CHAPTER 1

SEPSIS AND SEPTIC SHOCK

Laennec in 1831 (1) and Boise in 1897 (2) noted the occurrence of a collapsed state in some patients with sepsis but not until 1951 was the clinical syndrome of shock associated with sepsis fully described by Waisbren (3) and Borden and Hall (4). Since then, many reports have been published on the incidence, clinical features, bacteriology, and therapy of septic shock, emphasizing the problem as one of increasing importance in the modern hospital environment.

Clinical features.

Bacterial invasion of the blood-stream from a local source of sepsis such as peritonitis, pyelonephritis, or an abscess is a common predisposing factor in the development of septic shock. In patients with bacteremia, approximately one-third develop a phase of shock. Hall and Gold (5) reported 100 patients with bacteremia due to a variety of organisms, of whom 35 were shocked, and Weil and his associates (6) in reviewing 692 patients with bacteremia due to Gram-negative enteric organisms, found that 169 (24%) had been hypotensive. This complication is both more common and more serious in the very young, the elderly, and in those patients debilitated by serious underlying pathology.

The source of the bacteremia in about 50% of patients is

genito-urinary infection, especially following catheterization or instrumentation of the lower urinary tract (7), and biliary tract, intra-abdominal, and pulmonary sepsis are responsible for most of the remainder (8). As intravenous therapy is now a routine following operations of any magnitude, and as hyperalimentation is used increasingly to maintain certain patients' nutritional balance by giving fluids of high caloric content via indwelling venous catheter, reports of consequent septicemia are becoming more frequent. Bentley and Lepper (9) reported that indwelling venous catheters were the causative factor in 19 of 44 patients with hospital-acquired septicemia, and Darrell and Garrod (10) describe 3 patients who developed septicemia associated with indwelling venous catheters through which antibiotic chemotherapy was being given.

Septic shock has also been described following transfusion of contaminated blood, and in this event the organism responsible may be one which can grow at 4°C and which is normally non-pathogenic in man. Borden and Hall (4) described a patient with septic shock following transfusion of blood contaminated with organisms of an achromobacter species, and Black and his colleagues (11) reported a similar case due to Serratia marcescens.

The patient with a severe septic lesion is usually pyrexial,

with a raised pulse rate, warm extremities, and hyperventilation. The increased ventilation leads at first to respiratory alkalosis, with low arterial pCO_2 and raised pH. When shock develops, as diagnosed by the generally accepted criteria of arterial hypotension, metabolic acidosis, lactacidemia, and oliguria, the clinical features in approximately half of the patients become those of a progressive low flow state with a fall in cardiac output and a rise in peripheral resistance. In the remainder, however, the features of a hyperdynamic circulation are maintained until the terminal stages. MacLean (12), Siegel (13), and Blair (14) and their associates have all reported finding a hyperdynamic circulation in approximately one-half of their patients with septic shock. The hemodynamic patterns are discussed below in more detail.

The lung lesion.

In some patients with septic shock, a progressive lung lesion develops even when the lung is not the site of the primary septic process. Riordan and Walters (15) and McLean and his associates (16) have described the characteristic clinical and radiological findings of pulmonary edema in these patients but in 14 out of 17 cases (16) the central venous pressure was normal or low, indicating that cardiac failure is not the cause. Harrison and his colleagues (17) found increased permeability of the pulmonary capillaries and decreased pulmonary surfactant activity in experimental endotoxemia

in dogs and this mechanism would explain the edema of the alveolar septa which may, in turn, lead to pneumonitis, atelectasis, and pneumonia as secondary complications (18). Perfusion of unventilated alveoli may then cause arterial pO_2 to fall. McLaughlin and his associates (19, 20) discuss the serious derangements in ventilation-perfusion ratio which occur in shock. They found that 15% to 30% of pulmonary arterial blood may perfuse alveoli which are not ventilated and which therefore take no part in respiratory exchange. There is evidence that pulmonary fat embolism is an additional factor in the pathogenesis of the lung lesion in sepsis. Lipid pneumonitis has been demonstrated in dogs with peritonitis (18), and hypertriglyceridemia with pulmonary fat embolism have been found in dogs with septicemia induced by intravenous injections of coliform bacilli (21). Elevated serum triglycerides and free fatty acids have also been reported in patients with infections due to Gram-negative bacteria (22). In explanation of these findings, it has been postulated that catecholamine release in bacteremia results in mobilization of fat which is inadequately handled by the liver with consequent release of free fatty acids and triglycerides into the hepatic vein.

Notes on the etiological role of endotoxin.

Endotoxin is a complex lipopolysaccharide constituent of the O-somatic antigen which is loosely attached to the cell walls of

Gram-negative bacteria (23). There is little doubt that all of the following terms, which have been used by various investigators to describe the material now known as endotoxin, are synonymous: Shwartzman material; Boivin antigen; toxic lipopolysaccharide; tumor necrotising agent. Purified endotoxin may be prepared by phenolic extraction of Gram-negative bacteria and ultracentrifugation of the extract (24). Several commercial preparations of this material are available.

Many investigators noted the similarity between the pathophysiology of shock experimentally induced with endotoxin preparations and shock due to sepsis. Over the last fifteen years a large volume of work has been published on experimental endotoxin shock in many animal species, of which rabbits (25), cats (26), dogs (27, 28) and primates (29, 30) have received most attention. There are, however, considerable differences among different species in the effects of endotoxin (31). It is also important to note that the effects of whole live Gram-negative bacteria are similar but not identical with the effects of purified endotoxin. In the dog, for example, which has been the most intensively investigated animal, live organisms do not cause the precipitous fall in arterial blood pressure, the rise in portal pressure, and the rise in total peripheral resistance, all of which occur after endotoxin (32, 33).

In addition, endotoxin cannot be incriminated in the pathogenesis of shock due to bacteremia with Gram-positive organisms as they do not have any lipopolysaccharide constituent similar to endotoxin. Experimental endotoxin shock cannot, therefore, provide an entirely satisfactory model to compare with septic shock in man, although there is no doubt that endotoxins are at least partially responsible for the syndrome.

For these reasons, the term "septic shock" is preferred to "endotoxin shock", and the experimental model to be described was designed accordingly.

Bacteriology.

Most cases of severe sepsis leading to shock have been due to Gram-negative bacteria although the Gram-positive bacteria may cause a similar syndrome. In recent years, bacteriological isolates from cases of septic shock have shown an increasing preponderance of Gram-negative organisms. In 1955, Hall and Gold (5) found that Staph. pyogenes was the causative organism in 30% of patients with septic shock, whereas in 1969 Baue (34) notes in a review article that this organism was responsible in less than 10% of cases. This changing pattern has been brought about by a number of factors such as the increased number and variety of major surgical procedures which are now possible, and the increased use of antibiotic chemotherapy to

which the Gram-negative organisms have proved more resistant. As has been mentioned, the elderly patient is more likely to develop septic shock as a complication of sepsis and as anesthetic skills have grown, so have the opportunities to carry out necessary operative procedures on relatively high-risk patients. Septic complications in elderly patients, especially if they are undergoing abdominal or urological procedures, tend to be due to Gram-negative organisms.

In approximately 50% of patients with septic shock due to the Gram-negative organisms, Escherichia coli or paracolon bacilli are isolated, although there is now an increasing number due to the Klebsiella-Aerobacter group, Proteus and Pseudomonas species (8, 35). Achromobacter and Serratia species have been mentioned as organisms which are normally non-pathogenic yet can cause septic shock if they contaminate blood for transfusion (4, 11). In these cases, the shock syndrome is almost certainly caused by the endotoxin already contained within the transfused blood as the organisms cannot grow at body temperature.

Treatment.

In the management of septic shock, recent experience has demonstrated the prime importance of clinical evaluation of the adequacy of blood volume by measurement of the central venous pressure. MacLean and his associates (36, 37) have emphasized the

usefullness of central venous pressure measurement as a guide to the necessary rate and volume of intravenous therapy. Many cases of "refractory shock" have been found to respond to intravenous infusion of blood, plasma, or even crystalloid solutions until a high normal central venous pressure is achieved, even when there was no evidence of pre-existing blood or fluid loss. The explanation of this finding is the increased blood volume requirement of an abnormally expanded peripheral vascular bed.

The role of antibiotics in controlling the septic source is undisputed and in most cases treatment must be commenced with a broad-spectrum drug until results of bacteriological culture and the organism's antibiotic sensitivity are available.

Arterial pO_2 and pH must be measured, and oxygen and intravenous bicarbonate may be required in an attempt to correct reduced levels.

Very little controversy persists on the relative merits of vasoconstricting and vasodilating drugs. It is now well established that temporarily raising the arterial blood pressure by constricting peripheral arterioles reduces tissue perfusion thereby intensifying the basic problem of organ dysfunction, and confers no benefit on the patient. Walters and McGowan (38), Weinstein and Kainer (39), and many other authors have recommended abandoning the use of norepinephrine in clinical septic shock and this opinion currently prevails. Irving (40) has conclusively demonstrated the deleterious

effects of sustained sympatho-adrenal hyperactivity in hemorrhagic shock and these effects are probably produced by norepinephrine therapy in septic shock. Hodgin and Sanford (41), reporting on 38 patients with shock due to Gram-negative bacteria, found a higher mortality in patients given vasopressor agents than in those not so treated.

Isoproterenol has certain pharmacological effects which theoretically commend its use. As a beta-adrenergic stimulant it increases the stroke volume and heart rate, and lowers the total peripheral resistance (42). These changes cause increased tissue perfusion. Siegel and Fabian (43) found that isoproterenol decreased renovascular resistance in endotoxin shock in dogs, and Starzecki and his associates (44) using a similar model, found that isoproterenol reduced mortality and caused a significant increase in urine flow. In clinical practice, isoproterenol infusion together with the necessary fluid volume therapy to maintain the central venous pressure have proved valuable. Patients with septic shock are usually given a great multiplicity of therapeutic agents, and it is therefore difficult in any small series of cases to attribute a beneficial effect to one particular agent. However, Du Toit (45) described 5 patients successfully treated with isoproterenol, and Kardos (46) noted improvement in

the clinical condition of 12 patients with septic shock when isoproterenol was substituted for metaraminol in the therapeutic regime.

Phenoxybenzamine is an alpha-adrenergic blocking drug which has been shown to be useful in the management of experimental endotoxin shock in dogs (47) and in primates (48), and Anderson and his associates (49) noted clinical benefit with increased cardiac index and increased urinary output in 4 patients with septic shock treated with phenoxybenzamine.

Melby and Spink (50) found that there was adequate endogenous steroid production in septic shock but there is considerable clinical and experimental evidence that large pharmacological doses of steroid are beneficial (51, 52). The glucocorticoids exert their beneficial effect by causing peripheral vasodilatation and myocardial stimulation, with consequent raised cardiac output. In addition to these hemodynamic effects, Schumer and Nyhus (53) in a survey of the role of corticoids in shock note that steroids stimulate glucogenesis and adenosine triphosphate production, and there is evidence that they enhance lysosomal membrane stability which may be impaired by circulating endotoxins. Weissmann and Thomas (54) studied the effects of endotoxin and glucocorticoid on the release of beta-glucuronidase and cathepsins from rabbit liver. They found that

five minutes after endotoxin administration there was augmented release of these lysosomal acid hydrolases but that pretreatment with steroid prevented the endotoxin effect.

Chlorpromazine is also known to stabilize lysosomal membranes, and this may partially explain the clinical benefit which has been reported following its use in patients with septic shock (55), although its effect in lowering peripheral resistance is also important.

Blair and his associates (56) have used hypothermia in 45 patients in septic shock, with a slight reduction in mortality, but this form of therapy is not suitable for widespread application.

Prognosis.

The overall prognosis in septic shock is grave, with mortality rates ranging from 25% to 80% in reported case series (5, 6, 8, 12). The mortality is highest in neonates, in patients over 60 years of age, and in debilitated patients.

Gluck and his associates (57) reported a 44% mortality in septicemia of the new-born, and Lewis and Fekety (58) found an increasing mortality associated with increasing age in 393 patients with bacteremia due to Gram-negative organisms. In an analysis of 860 patients with bacteremia due to Gram-negative organisms at the University of Minnesota Medical Center, Dupont and Spink (35)

reported that the mortality increased from 23% in patients who were in good health before developing the septic lesion to 88% in those patients developing bacteremia as a complication of severe burns, leukemia, or carcinomatosis.

THE METABOLIC EFFECTS AND OXYGEN CONSUMPTION

The most striking metabolic derangements in clinical septic shock are the progressive increase in blood lactate, and decrease in pH, associated with decreased arteriovenous oxygen difference, and decreased oxygen consumption (59). A significant inverse correlation has been found between oxygen consumption and blood lactate: the lower the oxygen consumption, the higher the lactate. It is known that hyperventilation alone can increase the blood lactate (60), but no correlation was found between arterial pCO_2 and arterial blood lactate in these patients (59). These changes tend to progress inexorably and no way of increasing the oxygen consumption has been found. Raising the arterial pO_2, either by increasing the inspired oxygen concentration (61) or by hyperbaric oxygenation (62) has not been helpful in clinical septic shock.

In experimental animals, endotoxins have been shown to alter glucose metabolism profoundly, decouple oxidative phosphorylation thus inhibiting the synthesis of adenosine triphosphate, and produce malfunction of the Krebs tri-carboxylic acid cycle (63).

Takeda and his associates (64) found that the administration of adenosine triphosphate prevented death in mice given a dose of Salmonella organisms which was usually lethal. In rabbits given a small dose of these organisms, there was usually a rise in blood lactate and a fall in alpha-ketoglutarate, and these effects were also prevented by adenosine triphosphate. Berry and his colleagues (65) found that the increased glyconeogenesis normally induced in mouse liver by cortisone was prevented by endotoxin. When rat liver mitochondria are incubated with pyruvate, citrate, or alpha-ketoglutarate substrate, the presence of endotoxin in the medium reduces the oxygen uptake (66), indicating inhibition by endotoxin of the normal mitochondrial oxidative mechanisms.

The hemodynamic changes.

The raised, bounding pulse rate, the warm extremities, the fever, and the hyperventilation observed in patients with severe sepsis are evidence of a raised circulatory requirement. The cardiac output is normal or high, and the total peripheral resistance is low (67). These hemodynamic changes seen in humans are less commonly seen in experimental animals with severe sepsis. Using purified endotoxin in the dog, a collapsed low-flow state is invariably produced which bears no relation to the high flow state observed in so many patients with sepsis. However, two experimental models in the dog have been described in which a hyperdynamic

circulatory state does develop in response to sepsis. Clowes and his associates (18) described a satisfactory model in which a hyperkinetic circulation accompanies generalized septic peritonitis produced by ligation of the cecum, and Hermreck and Thal (68) observed the same response to creation of a septic abscess in a hind-limb.

As previously mentioned, a proportion of patients who develop shock complicating sepsis maintain this hyperdynamic circulation, as determined by raised cardiac output and the clinical findings, even with a lowered arterial blood pressure. Total peripheral resistance is reduced, the arteriovenous oxygen difference is narrowed, and oxygen consumption is low. This group of patients, in whom a blood volume or cardiac deficit is either absent or has been corrected, proves most refractory to therapy.

CHAPTER 2

WHAT IS THE BASIC LESION IN SHOCK DUE TO SEPSIS?

On the basis of the changes noted above in the oxygen consumption, the arteriovenous oxygen differences, and the hemodynamics,the possible factors or combination of factors which could lead to the coexistence of high flow with low oxygen extraction must be discussed.

1. Pre-capillary arteriovenous shunts.

It is possible that the increased cardiac output is being largely channelled through pathological arteriovenous shunts, thus causing relative ischemia of the capillary beds which in turn could explain the defective oxygen extraction and the lactacidosis. It is well known that physiological arteriovenous shunts do exist in many tissues, for example in skin (69), in the mesentery, and in the wall of the small intestine (70). One of the physiological mechanisms by which the body responds to a sudden demand for increased tissue perfusion is the closure of these shunts with consequent increased perfusion of the distal capillary bed.

Although direct evidence is lacking, many investigators have postulated that these shunts open abnormally, or that new pathological arteriovenous shunts develop to explain the hemodynamic and metabolic changes of septic shock (13, 67, 71, 72), and this view is most widely accepted at present. No evidence is available, however, on the relation of total flow to capillary flow, and it

is this relationship which is at the center of the controversy on the existence of pre-capillary arteriovenous shunts. One of the main purposes of the study to be described was to relate capillary flow to total flow in severe sepsis, and thus to obtain evidence on the question of whether pathological peripheral arteriovenous shunts exist or not.

2. Defective oxygen transport.

The transport of oxygen from environmental air to intracellular fluid depends on the following factors: ventilation of the lungs, the hemoglobin concentration in blood, respiratory exchange (alveolar/capillary) within the lungs, the arterial pO_2, the dissociation curve of oxyhemoglobin, and final diffusion of oxygen from the capillary to the cell. The lung lesion found in some patients with septic shock has been discussed, and it has been noted how resulting ventilation/perfusion abnormalities may cause a low arterial pO_2. It has also been noted, however, that in many cases the arterial pO_2 is normal or high but that the defective oxygen consumption persists (page 14). Low hemoglobin and hematocrit are not usually major problems in patients with septic shock, and where indicated, blood transfusion will correct any deficiency.

Some interest has recently been focused on the role of 2,3 diphosphoglycerate (2,3 DPG) within the red cell in the maintenance of the oxyhemoglobin dissociation curve. 2,3 DPG is an intermediary metabolite which competes to some extent with oxygen for the binding sites on hemoglobin. A rise in the concentration of 2,3 DPG within the erythrocytes causes the oxyhemoglobin dissociation curve to swing to the right, while a fall in 2,3 DPG concentration swings the curve to the left. When the curve moves to the left of normal, the hemoglobin per cent oxygen saturation is higher for a given pO_2 (see Figure 15, page 56). Miller and his associates (73) reported that the 2,3 DPG level was low in clinical septic shock, and they postulated that this caused poor tissue oxygenation which in turn was the cause of the low oxygen uptake. However, the overall effect in vivo of the many factors which are known to influence oxyhemoglobin dissociation remains speculative. For example, raised body temperature, low blood pH, and raised arterial blood pCO_2 cause the curve to be shifted to the right, whereas changes of these factors in the opposite direction move the curve to the left (74). Forstner and his associates (75) found that adenosine diphosphate and adenosine monophosphate inhibit the synthesis of 2,3 DPG. The impaired synthesis of adenosine triphosphate in septic shock and experimental endotoxemia has already been discussed (63), and the fall in 2,3 DPG level may

therefore merely reflect the accumulation of adenosine diphosphate and monophosphate in the red cell as part of a widespread metabolic upset.

Except in those patients who develop the lung lesion in association with septic shock, it is unlikely that defective oxygen transport is primarily responsible for the metabolic consequences.

3. Primary cellular damage.

The changes observed could be produced by a defect of the cell's oxidative processes which renders it incapable of normal oxygen utilization even in the presence of normal or high perfusion by adequately oxygenated blood. It is then necessary to incriminate a cellular poison deriving from the infecting organism. As has been discussed above, there is evidence that Gram-negative bacterial endotoxin can affect the cell in this way, although it is not the only toxin which may do so.

In experimental endotoxin shock the importance of circulating vasoactive polypeptides such as serotonin, bradykinin and histamine, has been enphasized, and they are believed also to be important in septic shock (76). Their presence may reflect more severe cellular and lysosomal damage as the hemodynamic consequences of severe sepsis develop.

The role of platelet aggregation leading to intravascular clotting has been suspected for some time in the etiology of septic shock. Hardaway (77) reported finding widespread intravascular thrombi in patients with septicemia, and pointed out that this could result in hemorrhage either because the clotting factors were used up too rapidly (consumption coagulopathy) or because of autogenous activation of heparin and fibrinolysin. Evans and his associates (78) have demonstrated the importance of platelet-aggregation in the genesis of endotoxin shock in the rabbit. These disturbances of the coagulation mechanisms could be caused by damage to the platelets as the primary insult.

CHAPTER 3

EXPERIMENTAL DESIGN

In the experimental work to date on the relationship of peripheral blood flow and peripheral oxygen utilization, blood flow has been measured by flowmeter probes placed on the artery feeding the tissue under study, or deduced by assessment of the cardiac output and peripheral resistance. No information is available on the capillary blood flow of the periphery in sepsis, and yet only by measuring capillary blood flow directly can the existence of pre-capillary arteriovenous shunts be assessed. Capillary blood flow may be measured by the $Xenon^{133}$ clearance technique described below. Skeletal muscle was chosen as the peripheral tissue to be studied because it represents a large proportion of total body mass, and because it is readily accessible. The hind limb skeletal muscle flow was measured in order to compare flow with arteriovenous oxygen difference measured between femoral artery and femoral vein. This study was designed to compare peripheral capillary flow, oxygen uptake, peripheral oxygen extraction and cardiac output before and after induction of a severe septic lesion in dogs.

Note on the hemodynamics in skeletal muscle.

The normal physiological mechanism whereby skeletal muscle blood flow responds to tissue demands for increased perfusion is the intense arteriolar vasodilatation resulting from local

accumulation of metabolites produced by the working muscle cells (79). There is a great uncertainty as to the relative importance of the cholinergic vasodilator and adrenergic vasoconstrictor sympathetic nervous supply to skeletal muscle at rest (80), but during exercise the neural influence becomes negligible. Whether anatomical pre-capillary arteriovenous shunts exist in normal skeletal muscle or not is a controversial issue, but it is known that capillary surface area may increase fourfold during metabolic vasodilatation (81).

In the human, capillary blood flow in resting skeletal muscle as measured by the Xenon^{133} clearance technique is 1.5-2.5 ml/100 G/min., while after maximal exercise it increases to 40-50 ml/100 G/min. (82, 83). These figures are for capillary ("nutritional") flow only, as any flow which is passing through arteriovenous shunts or in any other way by-passing the capillary bed is not detected by the Xenon technique. It is therefore possible using this technique combined with the hemodynamic measurements to determine whether any pathological shunts are in operation sufficient to diminish tissue nutritional flow below normal resting levels.

Background on the Xenon^{133} technique for measuring blood flow.

Blood flow through a tissue may be measured by injecting either directly into the tissue or into its arterial supply an indicator which then disappears from the tissue at a rate determined by the blood flow only (84). Lassen and Munck (85), and Kety (86) have pointed out that the indicator must diffuse freely across cell membranes, and its relative solubility in blood and in the tissue under study must be known. Of the radioactive tracers which have been used in this way, namely Na^{24} (86), Kr^{85} (87), and Xe^{133} (82), the inert gases are most suitable for the following reasons: they diffuse readily across cell membranes; their solubility in tissue and in blood is dependent solely on the physical property of partition coefficient as they take no part in the exchange processes relevant to metallic and base ions; 95% of their content in venous effluent is released to the expired gases in one lung passage (88).

In view of these considerations, the local blood flow is a function of the clearance curve of the isotope from the tissue, and its tissue/blood partition coefficient. Conn (89) has measured the partition coefficients of Krypton and Xenon in various tissues.

The blood flow in absolute terms of ml. per 100 G of muscle tissue per unit of time may be calculated according to the

formulae established by Glass and Lassen and their associates (89, 90).

The formulae are based on the Fick principle

$$Q' = (Ca - Cv) \tag{1}$$

where Q is the amount of Xe^{133} in the muscle at any given time, and Q' is the first derivative of Q with respect to time. F is the blood flow in ml per minute in the tissue containing the isotope, Ca is the arterial concentration of Xe^{133} in microcuries (μc) per ml and Cv the venous concentration in μc per ml.

Let MBF = muscle blood flow in ml per 100 G tissue per minute.

$$MBF = \frac{100 \cdot F}{W} \quad \text{therefore} \quad F = \frac{W \cdot MBF}{100} \tag{2}$$

where W = the tissue weight in grams.

Inserting equation (2) for F in equation (1)

$$Q' = \frac{W \cdot MBF\ (Ca - Cv)}{100} \tag{3}$$

$$\text{therefore } MBF = \frac{100 \cdot Q'}{W(Ca - Cv)} \text{ ml/100 G/min} \tag{4}$$

Now the partition coefficient (λ) of Xenon in muscle tissue/blood is 0.70 i.e. $\frac{C\ muscle}{C\ blood} = 0.7$ (5)

where C muscle = the concentration of Xe^{133} in μc per G. of muscle, and C blood = the concentration of Xe^{133} in μc per ml of blood.

From equation (5) $C_{blood} = \frac{C_{muscle}}{0.7}$ (6)

substituting equation (6) in equation (4)

$$MBF = \frac{100 \cdot Q'}{W \cdot (0 - \frac{C_{muscle}}{0.7})} \text{ ml/100 G/min} \quad (7)$$

as the arterial concentration of the isotope is zero after cessation of the injection.

Therefore $$MBF = \frac{-70 \cdot Q'}{W \cdot C_{muscle}} \quad (8)$$

According to definition, $W \cdot C_{muscle} = Q$

Therefore $MBF = -70 \cdot \frac{Q'}{Q}$ ml/100 G/min (9)

Figure 1 is an example of a $Xenon^{133}$ clearance curve, after injection into muscle, on a direct scale.

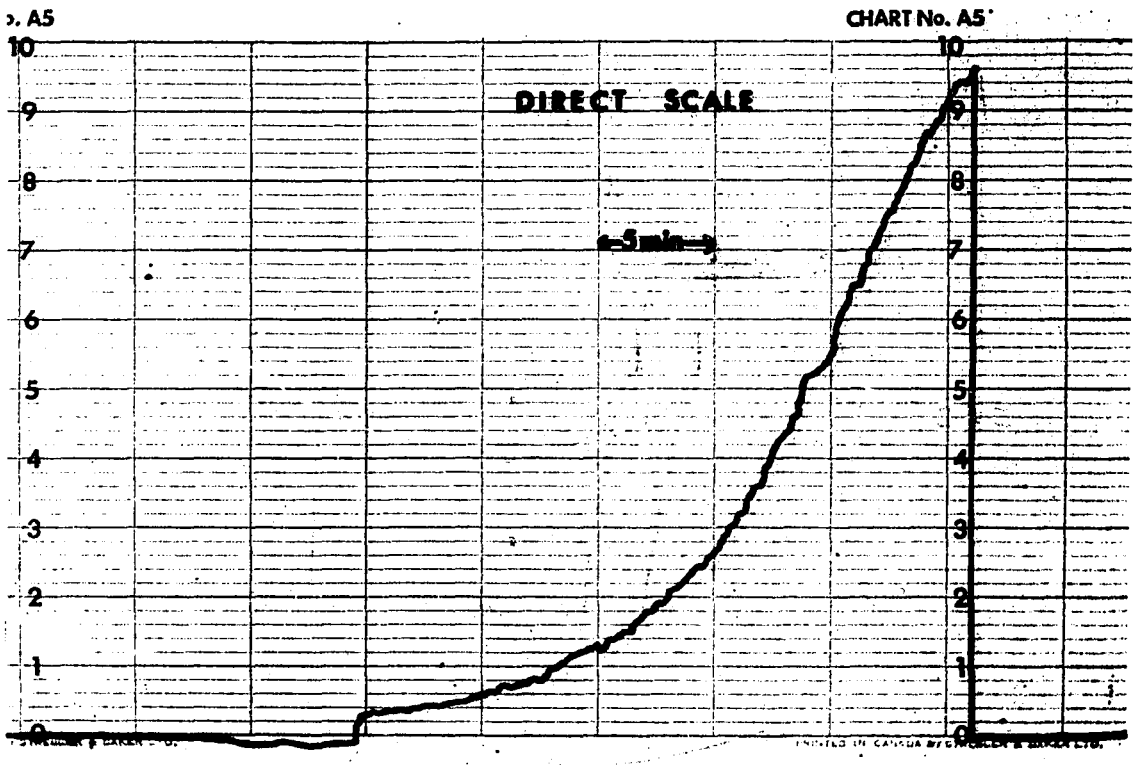

Figure 1. Xenon^{133} clearance curve on direct scale.

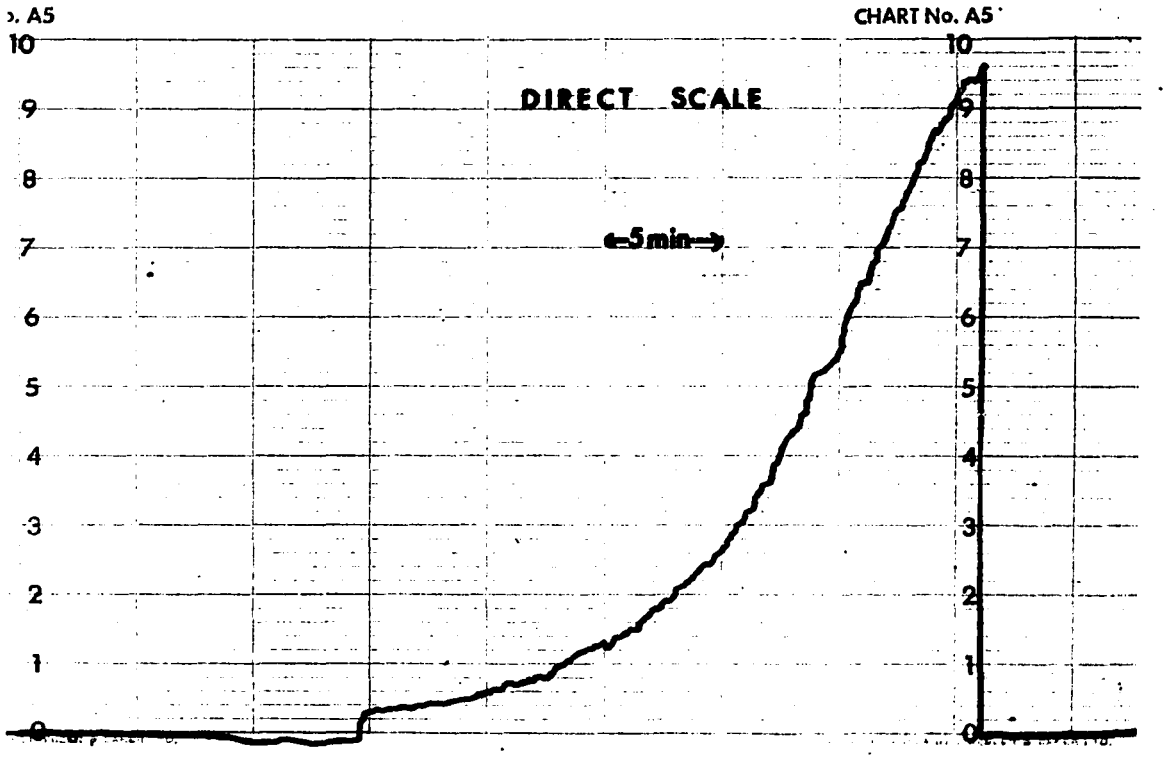

Figure 1. Xenon^{133} clearance curve on direct scale.

Since a logarithmic potentiometer may be used to chart the clearance curve of the Xe^{133}, the clearance rate $\frac{Q'}{Q}$ can be obtained from the tangent of the curve.

The slope of this tangent is $d \text{ Log}_{10} \frac{Q}{dt}$, since $\text{Ln } (10) \cdot d \text{ Log}_{10} \frac{Q}{dt} = d \text{ Ln } Q/dt = \frac{Q'}{Q}$, one obtains:

$$MBF = -70 \cdot \text{Ln}(10) \cdot d \text{ Log}_{10} \ Q/dt$$

$$= 161 \cdot D \ \text{ml/100 G/min}$$

where D is the fraction of one decade by which the tangent decreases in one minute (Figure 2).

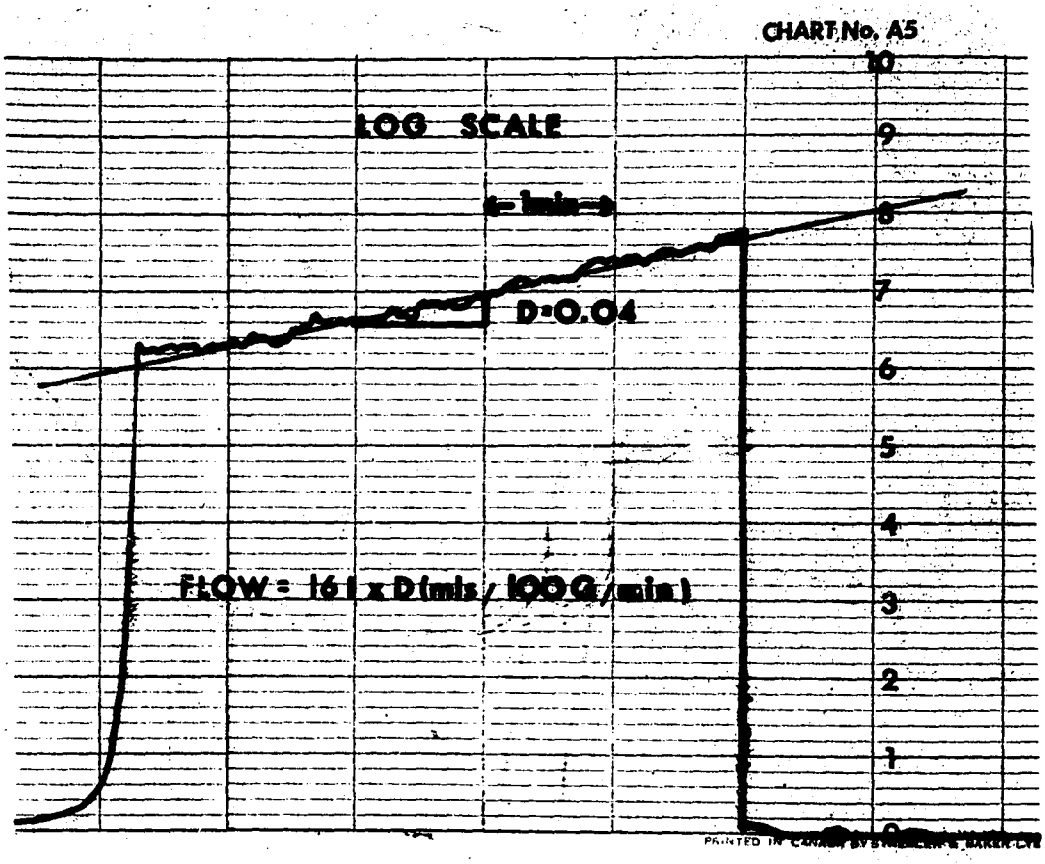

Figure 2. Xenon^{133} clearance curve on logarithmic scale.

Q cannot be observed directly; the observed counting rate is only proportional to Q. The above calculations show, however, that the required figure is Q'/Q which is observed in the clearance curve.

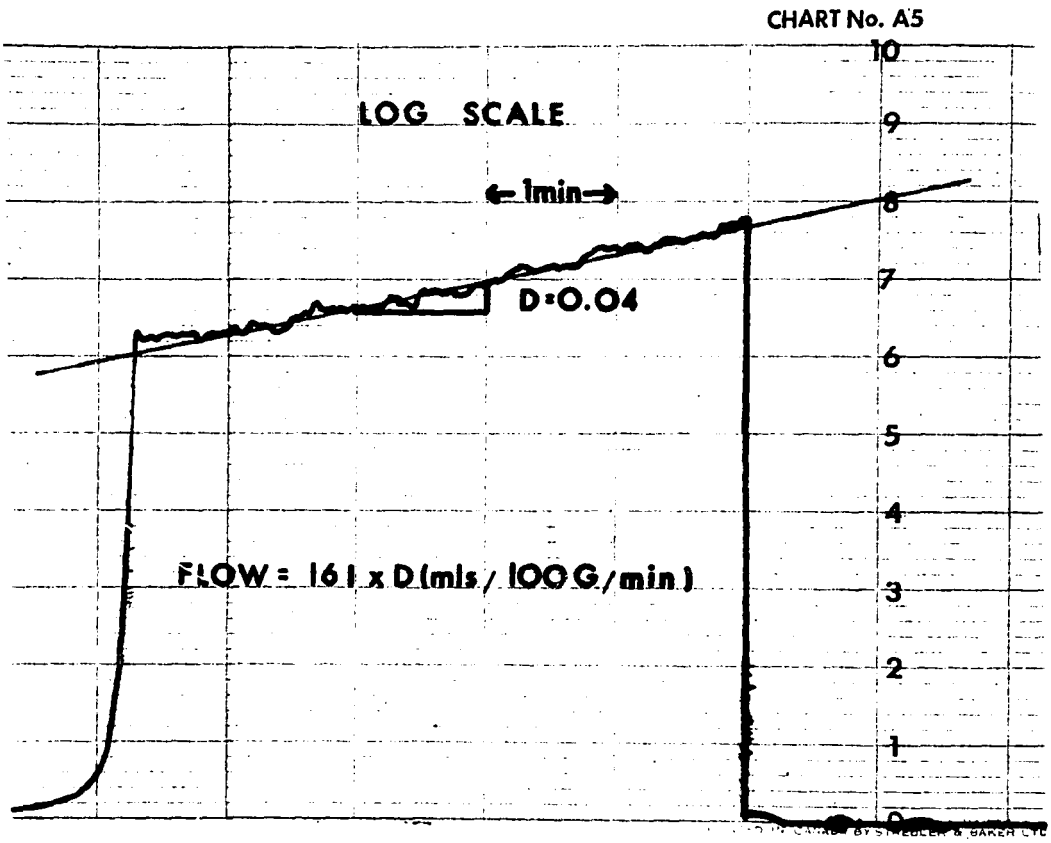

Figure 2. Xenon^{133} clearance curve on logarithmic scale.

Q cannot be observed directly; the observed counting rate is only proportional to Q. The above calculations show, however, that the required figure is Q'/Q which is observed in the clearance curve.

Kr^{85} is predominantly a beta-emitter with a maximum range in tissue of approximately 3 mm. Its use therefore necessitates placing the scintillation counter within about 1 mm range of the tissue under study. This is possible in some experimental models, and Kr^{85} has been used in this way to determine blood flow in the cerebral cortex (91), renal cortex (92), and gastric mucosa (93).

Xe^{133} is a soft gamma-emitter which may therefore be detected by a scintillation crystal at a distance of 10 cm or more from the source. Xe^{133} has been used in man to determine blood flow through skeletal muscle (90, 94, 95), the brain (96) and the renal cortex (97).

Xe^{133} is safe for use in the clinical situation, as it gives low energy radiation, and is rapidly eliminated from the body. In the case of skeletal muscle, for example, a blood flow determination requires the injection of about 50 μc of xenon which gives a gonadal radiation exposure of 0.02 millirads. Approximately 20 x 50 μc injections of Xe^{133} would be required to give a radiation exposure equal to one diagnostic chest x-ray (98).

Methods.

Twenty adult mongrel dogs of average weight 16.4 Kg. were lightly anesthetized with sodium pentobarbital, 20 mg per Kg. The right femoral artery was cannulated for arterial pressure recording and withdrawal of arterial samples. A catheter was inserted into the right atrium via the right femoral vein for central venous pressure

measurements. Through a cut-down on the right jugular vein, a catheter was inserted into the right ventricle for withdrawal of mixed venous blood samples. Rectal temperature was recorded.

Oxygen uptake was measured by collecting the expired gas, measuring the expired dried volume, and analysing for per cent oxygen by the micro-Scholander technique (99). Volumes were corrected to standard temperature and pressure, and oxygen uptake ($\dot{V}O_2$ in ml/min) then calculated from the formula:

$$\dot{V}O_2 = MV\left[\frac{F_eN_2}{F_iN_2} \times F_iO_2 - F_eO_2\right] \text{ mls/min}$$

where MV = expiratory minute volume;

F_eN_2 = expired nitrogen concentration;

F_iN_2 = inspired nitrogen concentration;

F_iO_2 = inspired oxygen concentration;

F_eO_2 = expired oxygen concentration.

The inspired gas in every case was room air.

Arterial blood pressure was recorded by a strain-gauge transducer and Sanborn recording apparatus. This system was calibrated immediately before each experiment using a mercury manometer.

Blood oxygen content was measured with the Van Slyke apparatus (100). Arterial tensions of oxygen and carbon dioxide and arterial pH were measured with an Instrumentation Laboratory Inc. blood gas analyser.

Blood lactate was measured in arterial samples by the colorimetric method of Barker and Summerson (101). Cardiac output was determined by the Fick principle from oxygen uptake and arterial/mixed venous oxygen difference.

To compare animals of various weights, body surface area in square meters was calculated using the formula

$$m^2 = Kg^{2/3} \times 0.112.$$

Cardiac index was expressed as liters per minute per square meter, and oxygen uptake as cubic centimeters per minute per square meter.

Total peripheral vascular resistance (TPR) was calculated in arbitrary units as follows:

$$TPR = \frac{\text{mean arterial pressure (mmHg)}}{\text{cardiac index (L/min/m}^2\text{)}}$$

Capillary blood flow in the left anterior tibial group of muscles was determined by the radioactive Xenon^{133} clearance technique. Fifty microcuries of Xenon^{133} dissolved in 0.1 ml of saline was injected into the muscle at a depth of about 2 cm using a 25 gauge needle and tuberculin syringe. Care was taken to ensure that the injection contained no bubbles. An external scintillation counter was then placed over the injected site, and the output fed from a ratemeter and logarithmic potentiometer onto recording paper. From the clearance curve of the Xenon^{133} thus obtained, the muscle capillary blood flow was directly calculated. In each experiment approximately

eight blood flow readings were taken from random sites in the muscle over a period of 30 minutes.

Blood was taken from the left femoral vein to measure the arterio-venous oxygen difference across the left hind limb while the muscle blood flow measurements were in progress.

After completion of these studies, a short midline abdominal incision was made and the cecum ligated 1 cm distal to the ileo-cecal junction so as to avoid any tendency to intestinal obstruction (Figure 3).

Figure 3. The ligature is placed round the cecum allowing free passage of intestinal content from ileum to colon.

The abdominal and cut-down incisions were then sutured, and the animal returned to its cage. One million units of benzyl penicillin were given intramuscularly 1 hour before ligation of the cecum, and daily thereafter to prevent the predominant growth of clostridia which would otherwise occur.

Five days later the dog was again lightly anesthetised, and all measurements recorded on the first occasion were repeated. Each animal, therefore, served as its own control before induction of the septic peritonitis by cecal ligation.

After all the measurements on the second occasion had been recorded, the dog was sacrificed by bolus intravenous injection of 750 mg of sodium pentobarbital. The abdominal cavity was then opened and inspected, and a swab taken of the peritoneal exudate for bacteriological examination.

An additional series of experiments was carried out to measure the changes in peripheral blood flow and oxygen extraction caused by muscle exercise. Five dogs were anesthetised as described (20 mg/Kg sodium pentobarbital) and muscle capillary blood flow in the left lower hind limb and femoral arteriovenous oxygen difference were measured. The muscles of the lower hind limb were made to contract by applying a 60 volt direct current for 10 milliseconds across the leg. This stimulus was repeated 10 times per second for 3 minutes, and immediately thereafter Xenon^{133} clearance

from the muscle and arteriovenous oxygen difference across the femoral vessels were measured.

The data were processed by electronic computer using a programme designed to calculate averages and standard deviations, and to carry out regression analyses and the paired t-test between variables.

CHAPTER 4

RESULTS

1. Sepsis.

All the animals subjected to ligation of the cecum were very ill by the 5th post-operative day with average temperature of 39.9 ± 0.4°C, hyperventilation, and lethargy. Severe peritonitis secondary to gangrene or perforation of the cecum was confirmed in every animal by postmortem examination after sacrifice.

Bacteriological examination of the peritoneal exudate in each case revealed a mixed flora of intestinal organisms, with Escherichia coli, Proteus species, and Enterococci predominating. On no occasion were any Gram-positive anerobic bacilli isolated, indicating that the penicillin therapy had been successful in suppressing the Clostridia.

The average fall in body weight in 5 days after induction of the peritonitis was 1.3 Kg.

None of the dogs was in shock at the time of the second experiment, but the mean arterial blood pressure fell from the control level of 150 ± 20 mmHg to 127 ± 19 mmHg. There were no significant changes in heart rate, central venous pressure or arterial pO_2 (Table I). A slight and insignificant fall in the hemoglobin level and in the hematocrit was observed. There was a significant rise in minute volume and fall in arterial blood pCO_2, and a highly significant rise in arterial blood pH. Figure 4 demonstrates the positive correlation between pH and minute volume.

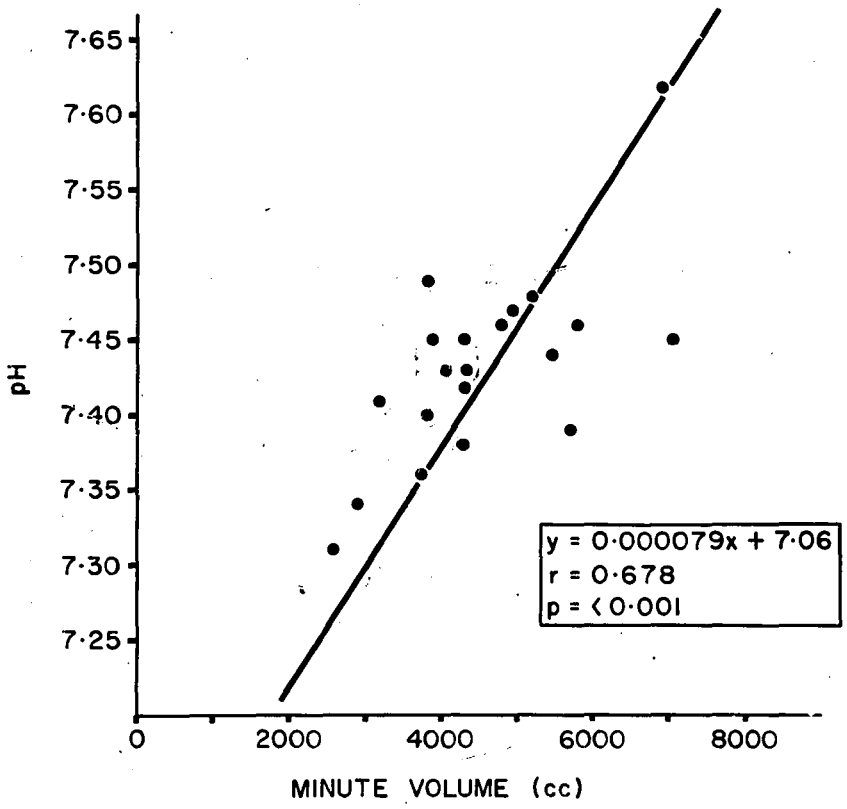

Figure 4. The rise in arterial pH found in the septic animals is significantly correlated with hyperventilation. The equation defines the line of best fit. 'r' is the correlation coefficient.

The arterial blood lactate was within the normal range in every case, and no differences could be demonstrated between the levels in the control and septic situation respectively. The rise in pH is not associated with any changes in the blood lactate as demonstrated in Figure 5.

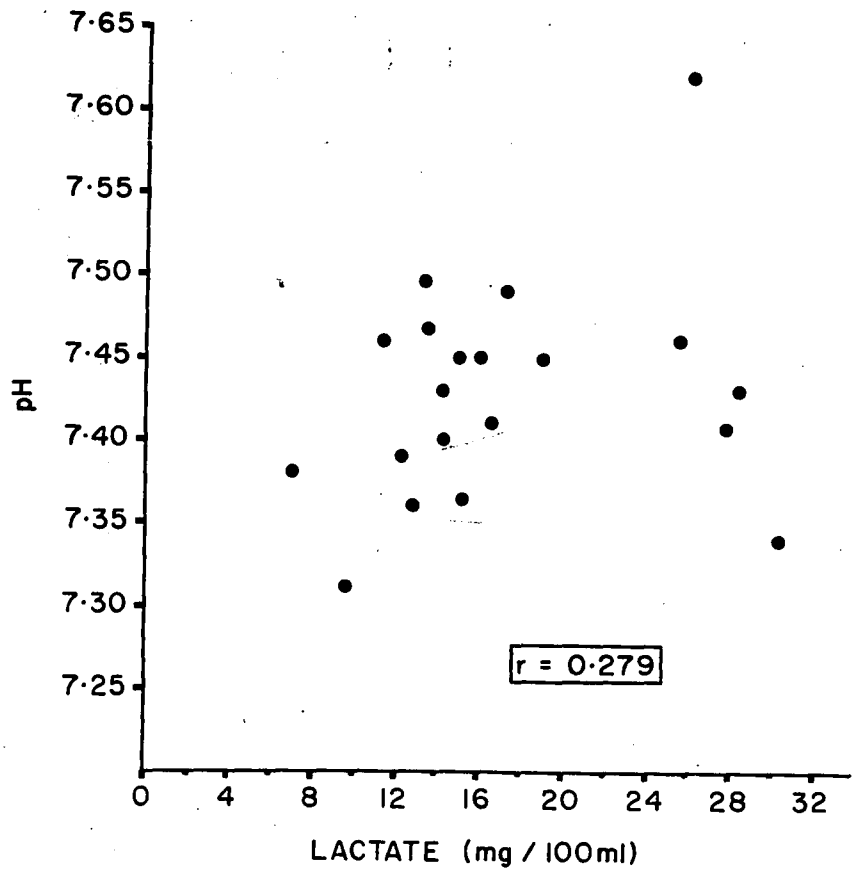

Figure 5. There is no correlation between arterial blood pH and lactate in the septic animals.

Two patterns of response to sepsis were found with reference to the changes in cardiac index, peripheral vascular resistance, muscle capillary blood flow, arteriovenous oxygen differences, and oxygen uptake (Table II). One group (9 dogs) responded with a normal or raised cardiac output, lowered peripheral vascular resistance, and narrowed arterial-mixed venous and arterial-femoral venous oxygen differences while the others (11 dogs) exhibited a reduced cardiac output, raised peripheral resistance, and widened arteriovenous oxygen differences. The cardiac index was found to correlate significantly both with the total and the femoral arteriovenous oxygen differences (inverse correlation). Figures 6 and 7 show the cardiac index plotted against the total and femoral arteriovenous oxygen differences respectively.

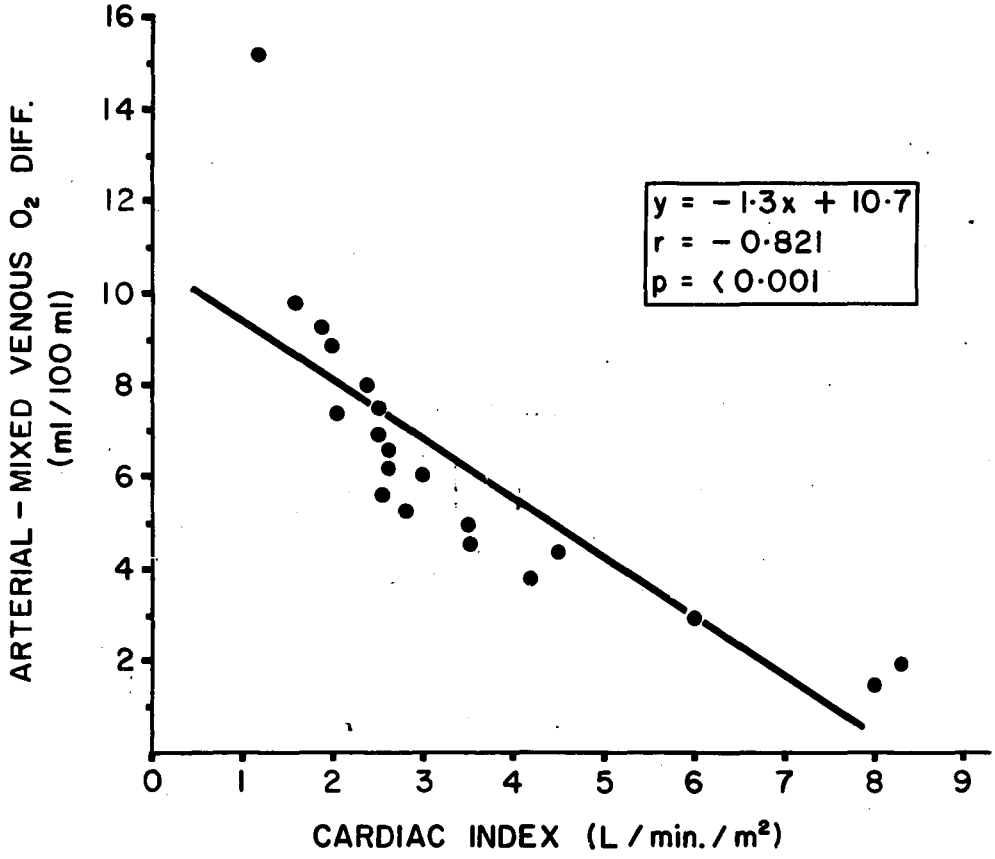

Figure 6. There is a highly significant negative correlation between the arterial-mixed venous oxygen difference, and the cardiac index. As the oxygen difference falls, the cardiac index rises.

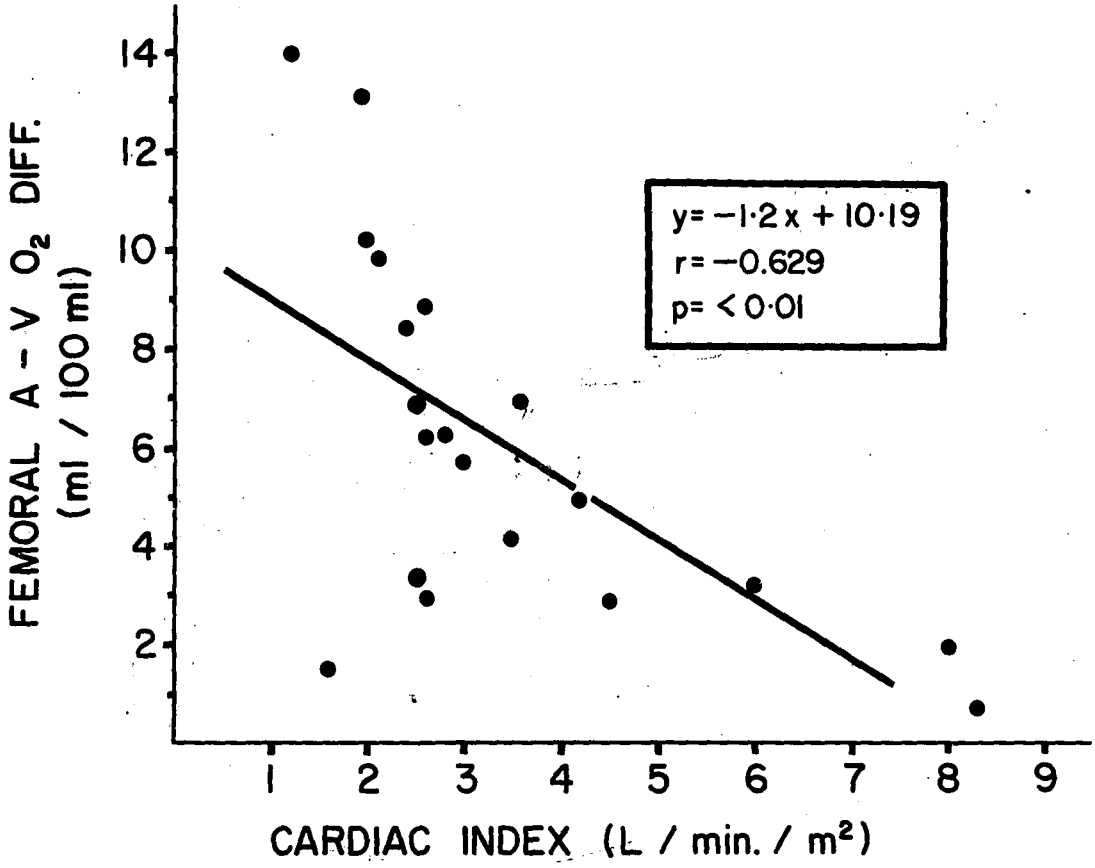

Figure 7. Narrow arteriovenous oxygen difference across the femoral vessels is associated with raised cardiac index.

Control resting capillary blood flow in the anterior tibial muscle group was 3.68 $\pm$ 1.83 ml per 100 G per minute, from 160 separate observations. In the hyperdynamic group there was a very large rise in muscle blood flow after induction of the septic model, but in the low output group there were variable inconsistent changes with a slight rise in the overall mean (Table II). In all the septic animals there was significant correlation between the cardiac index and the muscle blood flow (Figure 8) demonstrating that high cardiac output was associated with high capillary blood flow in skeletal muscle.

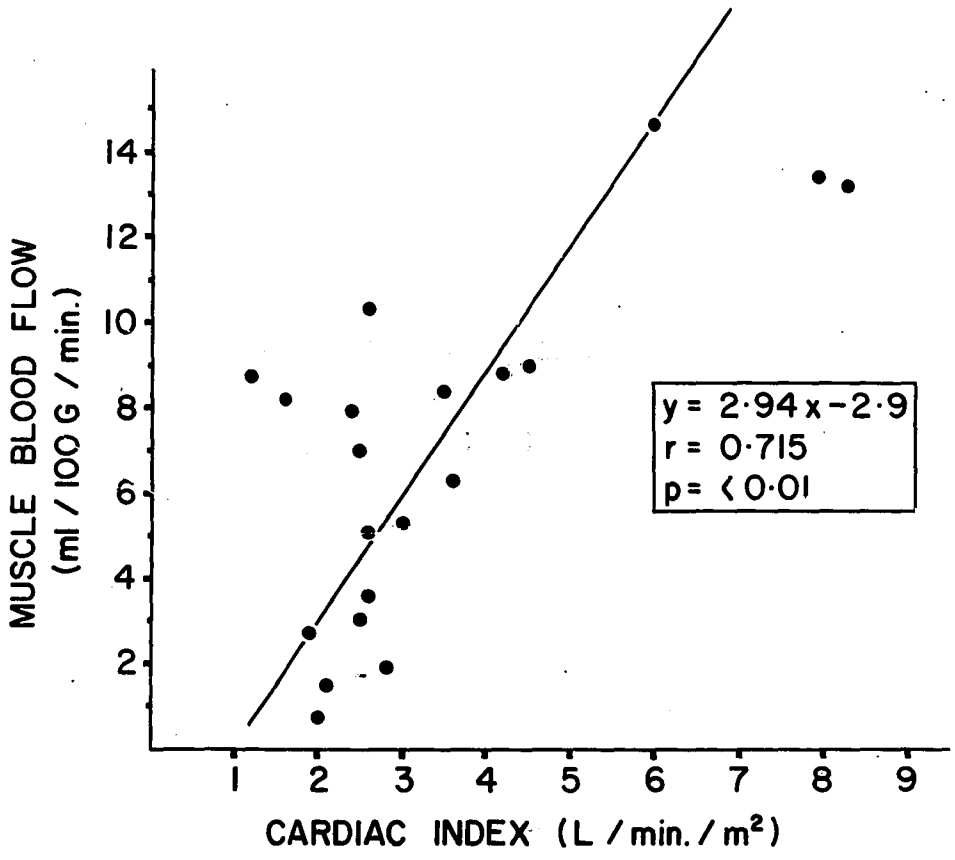

Figure 8. In all septic animals, there was a significant relationship between cardiac index and muscle capillary blood flow. As the cardiac index rises, so does the capillary flow.

When those animals who responded to sepsis with a hyperdynamic circulation were considered separately, the relationship between cardiac index and muscle blood flow was found to be highly significant (Figure 9).

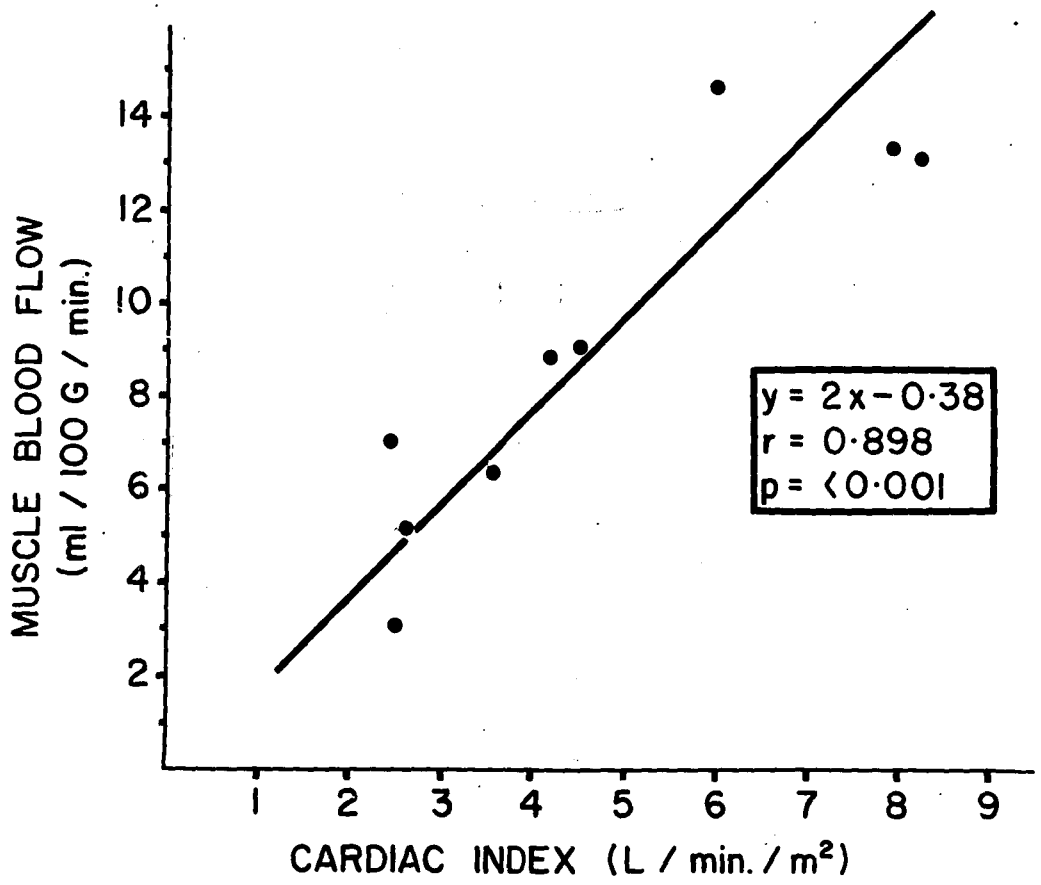

Figure 9. In the hyperdynamic septic group, the positive correlation between cardiac index and muscle capillary blood flow is highly significant.

Oxygen uptake in the low output group rose from the control level of 148 ± 19 ml/min/m^2 to 165 ± 12 ml/min/m^2. This was a significant rise ($p < 0.05$), whereas in the hyperdynamic group, oxygen uptake rose insignificantly from 154 ± 31 to 160 ± 28 ml/min/m^2.

When muscle blood flow was plotted against femoral arteriovenous oxygen difference in both septic groups, a significant inverse correlation was demonstrated (Figure 10); low arteriovenous oxygen difference was associated with high muscle blood flow.

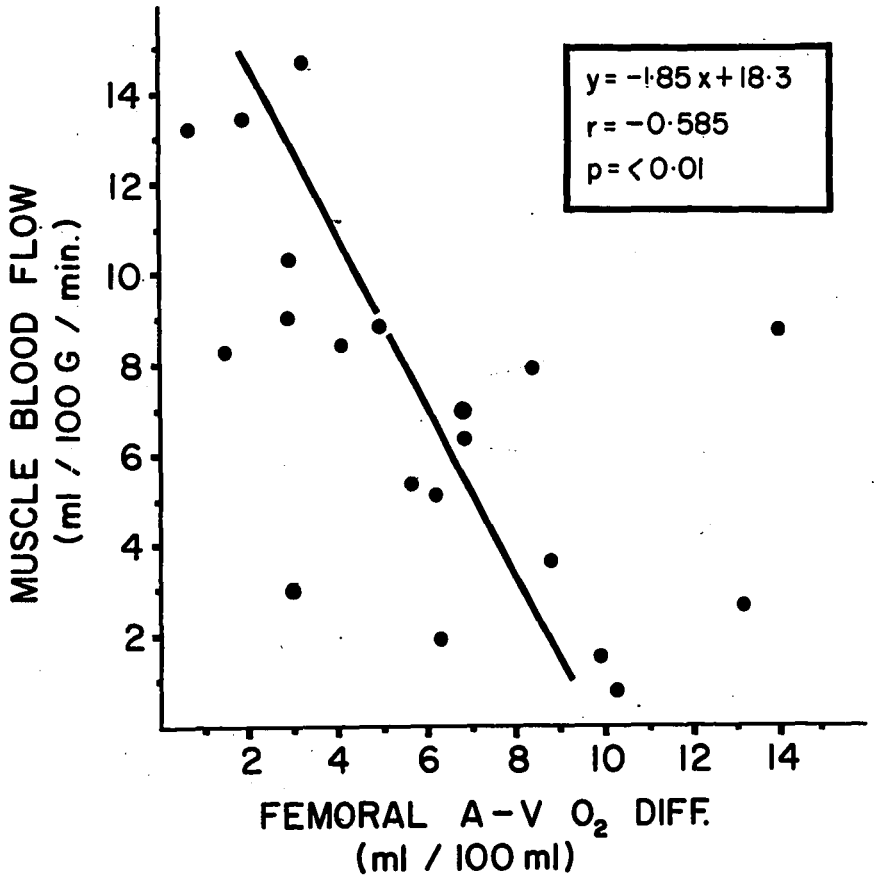

Figure 10. As the oxygen extraction across the femoral vessels decreases, the muscle blood flow increases (both septic groups).

2. Post-exercise.

Table III displays the individual measurements of femoral arteriovenous oxygen difference and muscle blood flow taken in the 5 animals who were examined before and after muscle exercise. Also displayed in Table III are the individual measurements for the hyperdynamic septic group before and after the septic lesion was produced. Table IV displays these results in summary form. The muscle blood flow was increased in both situations, but the changes in arteriovenous oxygen difference were in opposite directions. After exercise, the oxygen difference rose by 60%, but in sepsis it fell by 11%.

CHAPTER 5

DISCUSSION

In this series of experiments, the model in which septic peritonitis is created in dogs by ligation of the cecum has evoked in approximately 50% of cases a hyperdynamic circulatory response similar to that often seen in patients with septic shock. As has been discussed on Page 8 , this model is superior to that involving the administration of pure endotoxin (lipopolysaccharide) in which a low flow state bearing little relation to severe clinical sepsis is produced.

The absence of arteriovenous shunts.

Figures 8 and 9 (Pages 43 and 44) demonstrate that there is no arteriovenous shunting of blood in the septic animals' skeletal muscle in the experimental conditions described. As the cardiac output rises, the increased peripheral blood flow does pass through the capillary bed. It was seen in Chapter III that the Xenon clearance technique for measuring blood flow only measures tissue capillary flow, as any flow which is bypassing the capillary bed through pre-capillary arteriovenous shunts cannot take part in the process of Xenon diffusion from tissue to blood on which the technique depends. In none of the experiments was a raised cardiac index found to be associated with reduced capillary blood flow, as would be the case if pathological arteriovenous shunts of any significance were in operation.

Changes in skeletal muscle and whole body changes compared.

The relationship between arteriovenous oxygen difference across the femoral vessels and the arterial-mixed venous oxygen difference was almost linear (Fig. 11) and as demonstrated in Figure 8 (Page 43), the blood flow in the lower limb skeletal muscle was significantly correlated with the total body blood flow (cardiac index). It is unlikely, therefore, that the changes in the skeletal muscle bed are grossly different from those in the body as a whole, although the capillary blood flow was measured directly only in skeletal muscle.

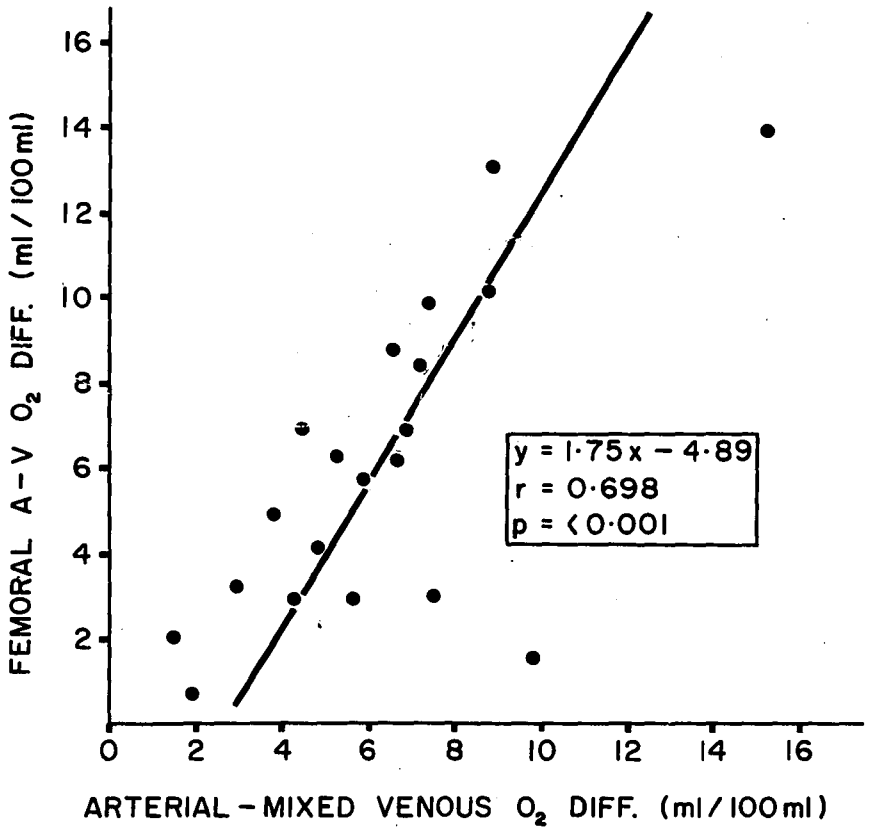

Figure 11. The correlation between the femoral and total arteriovenous oxygen differences was highly significant.

Alkalosis in septic shock

The alkalosis found in the septic dogs in this study was related to their increased respiratory minute volume (Figure 4, Page 37) and in this respect they are also similar to the patients with septic shock and a hyperdynamic circulation who often exhibit a respiratory alkalosis at first. MacLean and associates (12) have described the transition in these patients from a high output alkalotic state to a low output acidotic state, and they emphasized that the survival rate was improved when therapy was commenced during the alkalotic phase.

The response to increased tissue demand for oxygen.

A physiological demand for more oxygen, for example as in exercising muscle, is met by an increase both in blood flow and arteriovenous oxygen difference, whereas in sepsis there is increased flow but decreased oxygen extraction (Table IV, Figure 12). The relationship between low arteriovenous oxygen difference and high muscle blood flow seen in Figure 10 (Page 45) does not permit a conclusion as to cause and effect. Either one may cause the other, or both changes may be due to a third factor. One possible interpretation is that the muscle capillary bed is passively transmitting an increased cardiac output which is due to the increased demands of the septic area alone. It has been shown,

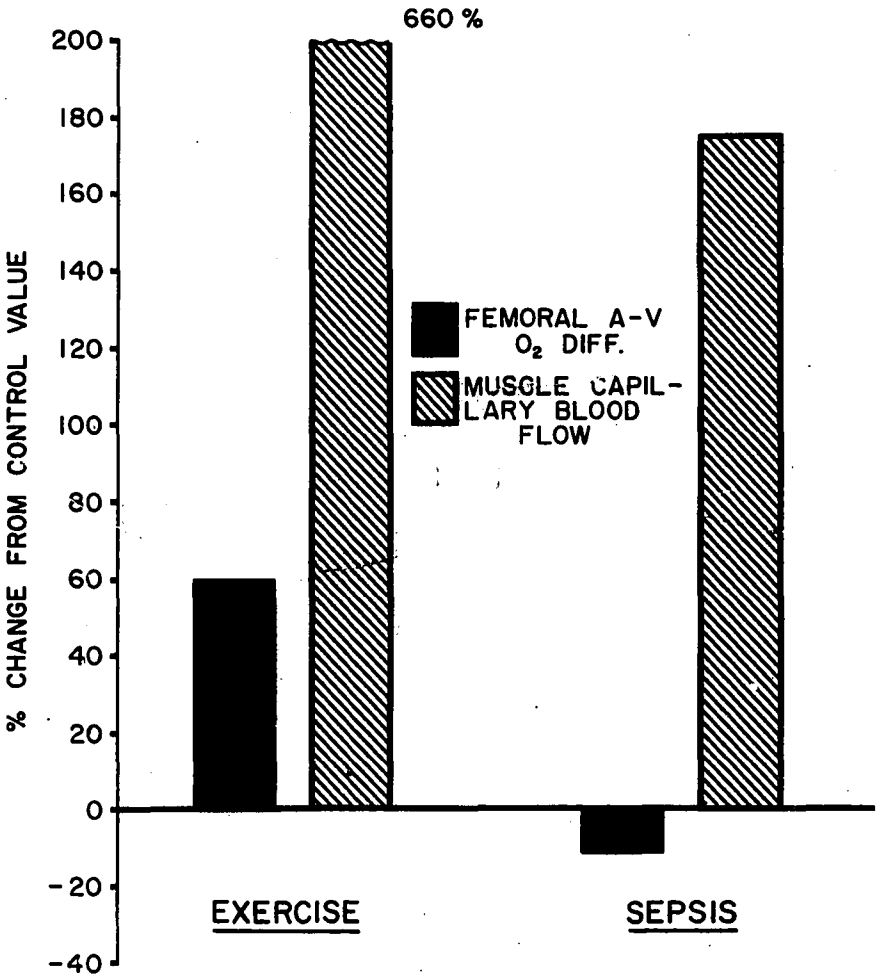

Figure 12. After exercise, both oxygen extraction and muscle blood flow increase, but in sepsis the oxygen extraction is reduced.

however, that an efficient blood flow regulatory mechanism exists in muscle, and it is therefore difficult to explain why a normal muscle should choose to intensify the cardiovascular problem by taking increased flow, when a normal physiological response would demand the opposite. It is more likely that the high flow is a secondary response to some change in the cells which has led to the reduced arteriovenous oxygen extraction, but this will be discussed in more detail below. Glass and his associates (88) have shown that a rise in arterial pCO_2 causes increased cerebral blood flow due to a direct vasodilator effect, but Figure 13 demonstrates that there was no relation between pCO_2 and muscle blood flow in this study.

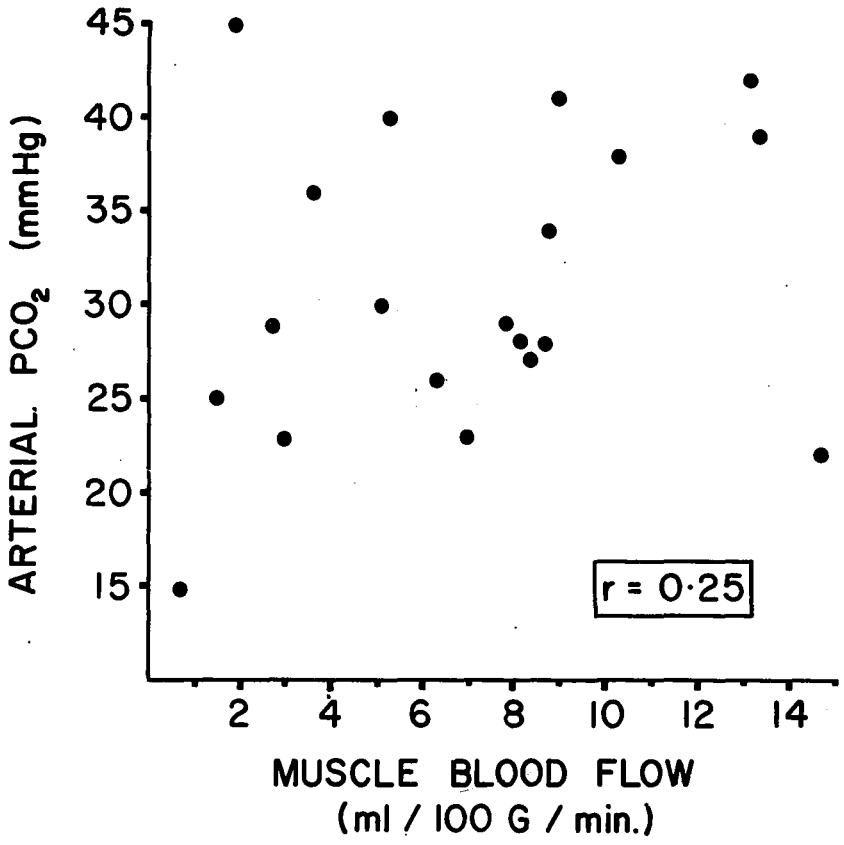

Figure 13. The changes in muscle blood flow in the septic animals were not associated with changes of carbon dioxide tension.

THE PRIMARY LESION

In Chapter II, the evidence and current opinions as to the basic lesion which is responsible for the hemodynamic and metabolic changes in septic shock were discussed. With the evidence presented in this study, the points discussed in Chapter II will be reconsidered.

1. Pre-capillary arteriovenous shunts.

Hermreck and Thal (72), Siegel (13), and Cohn (71) and their associates, who have argued the case for the importance of arteriovenous shunts, did so on the basis of the high cardiac output, low peripheral resistance and low arteriovenous oxygen extraction. It has been shown that these changes may also be due to cellular damage, and this study has presented direct evidence against the concept of shunting.

2. Defective oxygen transport.

The hemoglobin level, hematocrit, and arterial pO_2 were satisfactory throughout the series of experiments (Table I). Figure 14 shows that there was no correlation between the arterial pO_2 and the muscle blood flow. The other factor which could affect oxygen transport to the cell is the position of the oxyhemoglobin dissociation curve. In Figure 15, the various factors which

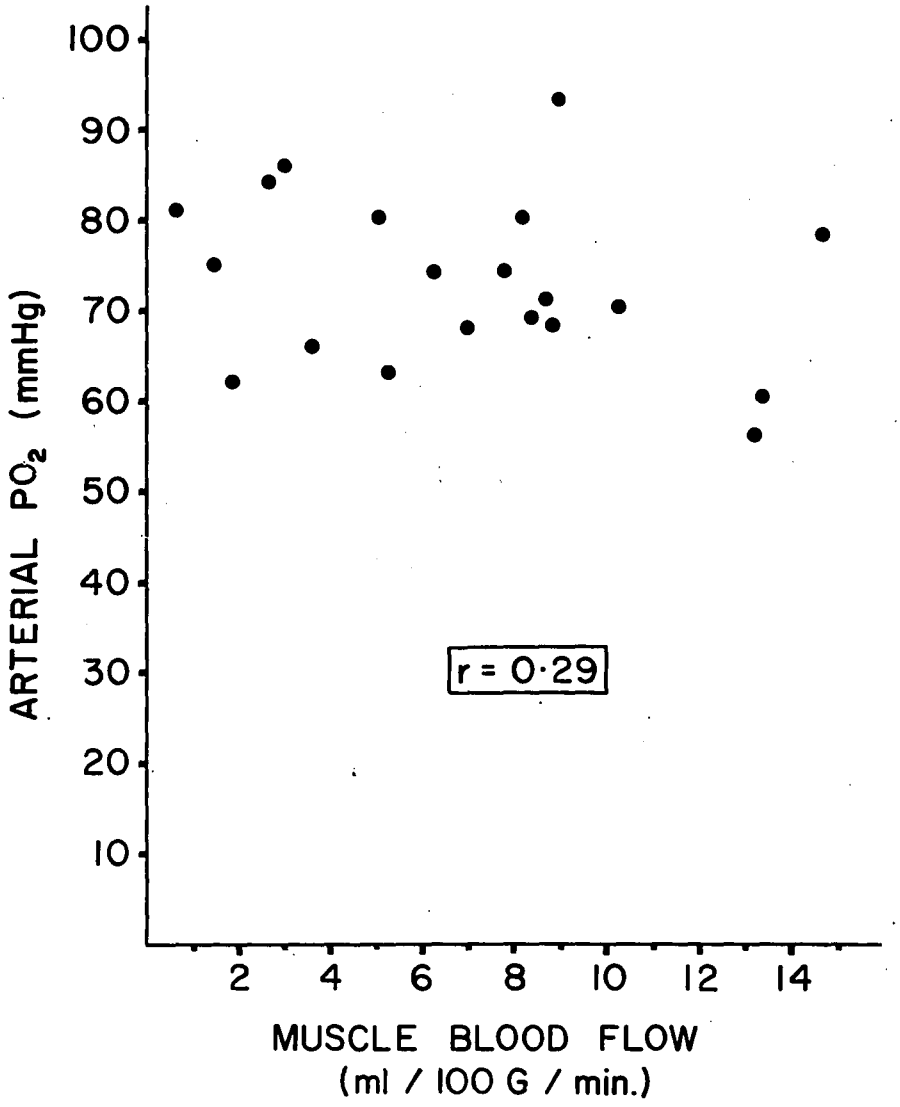

Figure 14. In the septic animals, the pO_2 remained adequate, and was unrelated to the changes in muscle blood flow.

influence the oxyhemoglobin dissociation curve, and the direction of their influence are shown. The level of 2,3 diphosphoglycerate was not measured in this study, and it would be impossible to speculate on the collective effect of all the factors on the position of the dissociation curve in vivo.

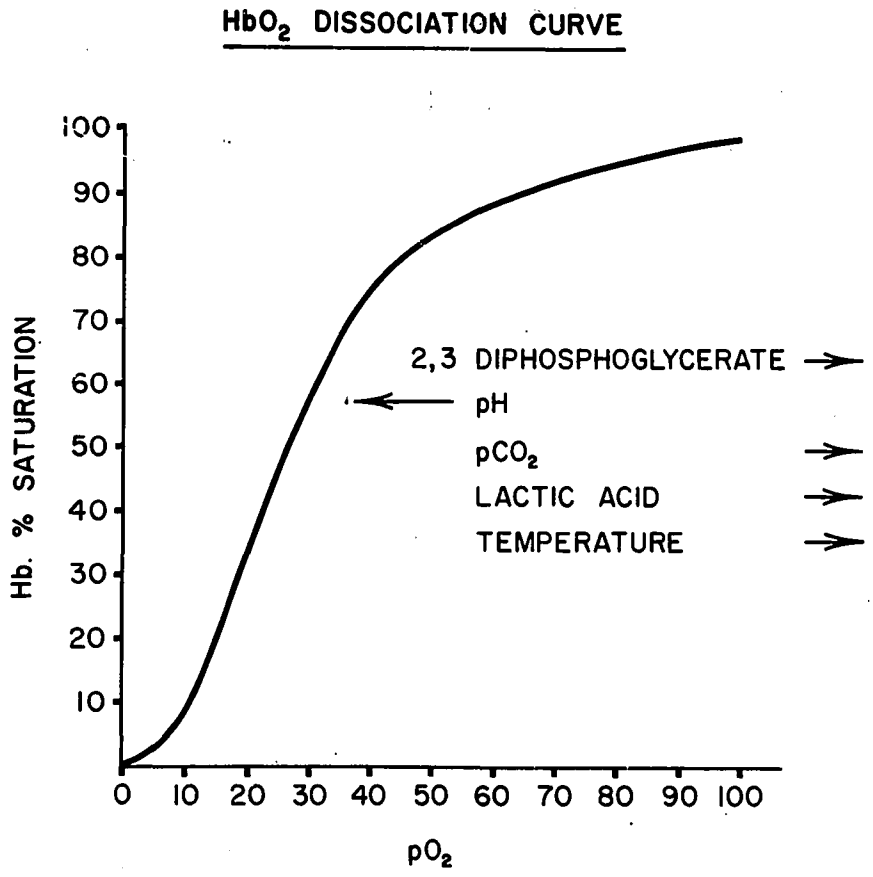

Figure 15. Factors known to influence the HbO_2 dissociation curve. For a rise in each value, the arrow points to the direction in which the curve is shifted.

3. Primary cellular damage.

The high cardiac output, high peripheral flow and low oxygen extraction found in this study are consistent with primary cell damage and subsequent attempted compensation by high capillary perfusion leading to relatively high tissue pO_2. The concept of primary cellular damage is also consistent with the release of vasoactive mediators as cellular and lysosomal damage progresses.

THE DIFFERENCE BETWEEN SEPTIC SHOCK AND OTHER TYPES OF SHOCK

It is becoming apparent that septic shock is fundamentally different from hypovolemic and cardiac shock. As depicted in Figure 16, the metabolic effects of hypovolemic and cardiac shock are due to poor tissue perfusion with consequent cellular hypoxia, while in septic shock a primary cellular defect probably exists due to circulating toxic bacterial products. The hemodynamic response which is at first compensatory, may later resemble the low flow situation seen in other types of shock as further cell damage occurs. The myocardium can only respond to a limited extent to the increasing circulatory demands of the body, and eventually cardiac decompensation takes place.

The study and management of shock has passed through two stages and is now entering a third. Fifteen years ago arterial hypotension was thought to be the first and most important manifestation of shock, and therapeutic efforts were devoted to raising

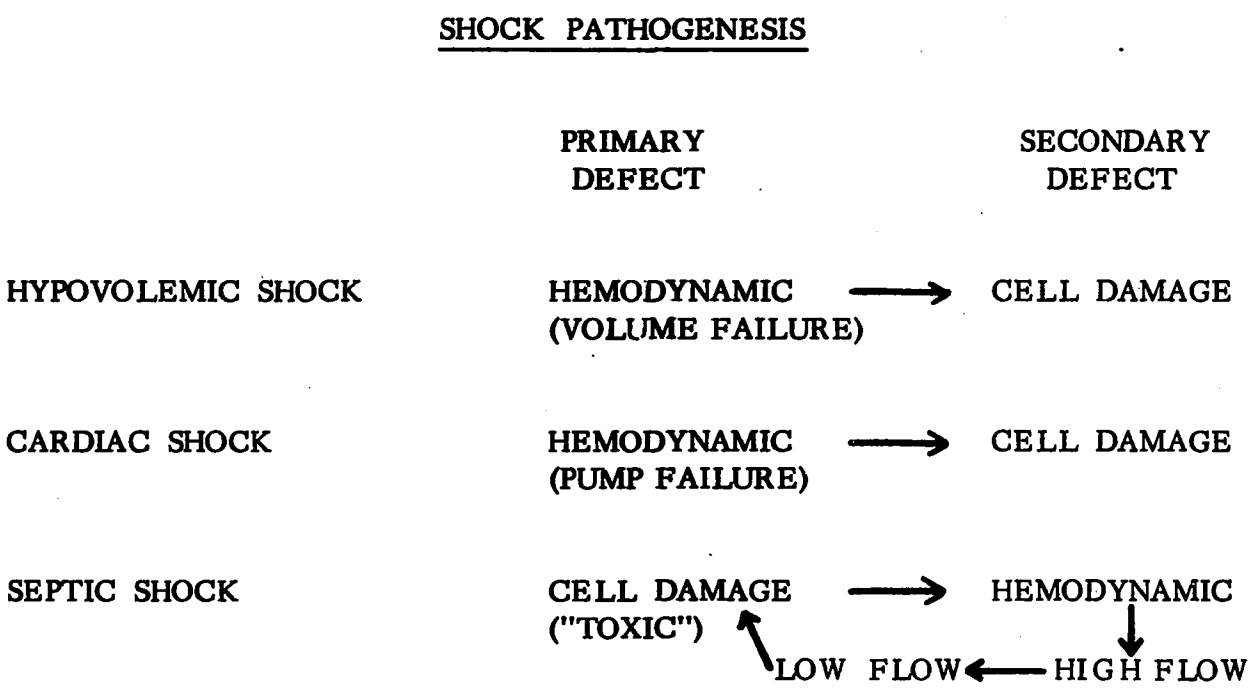

Figure 16. Diagrammatic representation of the different sequences of events in hypovolemic, cardiac, and septic shock.

the blood pressure irrespective of any other consideration. Later it was realized that adequate perfusion of tissue beds was vital in shock, and great advances were made in therapy designed to improve tissue perfusion by correcting blood volume deficiencies, relaxing deleterious peripheral vasoconstriction, and supporting heart action by the use of inotropic and chronotropic agents. At this point in the understanding of shock there was still the belief that if in some way the hemodynamic problems could be relieved the patient would recover. But there remained that baffling group of patients with septic shock who had normal or high tissue perfusion, who had no cardiac or blood volume deficit, and who were still unable to utilize oxygen normally. The evidence is now accumulating that these patients have a primary cellular defect leading to the hyperdynamic circulation as an attempted compensatory mechanism. This concept of the pathogenesis of septic shock explains the lack of response to therapy in this group of patients, and suggests that intensive biochemical studies on the subcellular metabolic processes in severe sepsis and septic shock would be required if effective therapy is to be found.

Summary and Conclusions.

The clinical findings, bacteriology, current status of therapy, and the prognosis of clinical septic shock were reviewed. The etiological role of Gram-negative bacterial lipopolysaccharide (endotoxin) was considered and the differences between the effects of endotoxin and the effects of whole live organisms in experimental preparations were emphasized.

The hemodynamic and metabolic findings in severe sepsis and septic shock were discussed, with special attention to the paradoxical combination of high peripheral flow and low oxygen consumption, which is found in some patients with septic shock. The possible mechanisms responsible for these findings were considered.

Using a model of induced sepsis in the dog, measurements were made of cardiac output, blood flow in skeletal muscle, oxygen uptake, and femoral and total arteriovenous oxygen differences. Control measurements were made in each animal before the septic lesion was created.

Half of the animals developed a hyperdynamic circulation, and there was highly significant correlation between the rise in cardiac index and increased muscle capillary blood flow, demonstrating that no pre-capillary arteriovenous shunts were present in this preparation.

The increase in muscle capillary blood flow was also related to narrowing of the total and femoral arteriovenous oxygen differences.

A further series of experiments demonstrated that after muscle exercise, muscle blood flow and the arteriovenous oxygen extraction both increased markedly, whereas in the septic state the increase in muscle flow was accompanied by a fall in oxygen extraction.

In hypovolemic and cardiac shock, low tissue perfusion and consequent tissue hypoxia produce secondary cellular damage. It is concluded that in septic shock this sequence of events is reversed; a primary cellular defect occurs, causing the hemodynamic disturbance as an attempted compensatory mechanism.

TABLE I

MEASUREMENTS BEFORE AND AFTER INDUCTION OF THE SEPTIC STATE

(average of results in 20 animals ± 1 standard deviation)

	Control	Septic	Change observed	p value
Weight (Kg)	16.4±2.6	15.1±2.4	- 8%	0.001
Temperature (°C)	37.8±0.4	39.9±0.4	+ 2.1°C	0.001
Arterial blood pressure (mmHg)	150±21	127±20	- 15%	0.01
Central venous pressure (cm H_2O)	11±2	10±4		N.S.
Heart rate (Beats/min)	170±18	170±16		N.S.
Hemoglobin (G/100 ml)	15.2±2.1	14.2±2.0		N.S.
Hematocrit (%)	45±6	42±5		N.S.
pH	7.33±0.05	7.43±0.06	+ 0.1	0.001
pO_2 (mmHg)	69±15	73±10		N.S.
pCO_2 (mmHg)	39±9	31±8	- 20%	0.02
Minute volume (L/min)	3.46±1.45	4.56±1.20	+ 32%	0.02
Blood lactate (mg/100 ml)	16.7±7.4	17.2±6.7		N.S.

N.S. = Not significant ($p > 0.05$)

TABLE II

COMPARISON OF HEMODYNAMIC AND OXYGEN UPTAKE RESULTS IN THE TWO GROUPS OF ANIMALS

(average ± 1 standard deviation)

	low output (11 dogs)			high output (9 dogs)		
	Control	Sepsis	p value	Control	Sepsis	p value
Cardiac index ($L/min/m^2$)	4.27±1.73	2.34±0.66	0.01	3.23±0.98	4.68±2.25	0.05
Peripheral Resistance ($mmHg/L/min/m^2$)	38.0±12.4	60.8±21.7	0.01	52.6±19.8	31.5±13.6	0.05
Muscle Blood Flow (ml/100 G/min)	4.03±1.95	5.40±3.44	N.S.	3.25±1.70	8.96±4.03	0.001
Femoral Arteriovenous O_2 difference (ml/100 ml)	4.77±3.3	7.72±4.0	0.01	4.60±1.8	4.08±2.2	N.S.
Total Arteriovenous O_2 difference (ml/100 ml)	3.87±1.1	7.77±2.9	0.01	5.03±1.2	4.44±2.2	N.S.
Oxygen Uptake ($ml/min/m^2$)	148±19	165±12	0.05	154±31	160±28	N.S.

N.S. = Not significant ($p > 0.05$)

TABLE III

MUSCLE BLOOD FLOW AND FEMORAL ARTERIOVENOUS DIFFERENCES IN THE HIGH OUTPUT SEPTIC GROUP, (9 EXPERIMENTS) AND AFTER EXERCISE (5 EXPERIMENTS)

EXERCISE				SEPSIS			
Femoral AVO_2 Diff.(ml/100 ml)		Muscle blood flow (ml/100 G/min)		Femoral AVO_2 Diff.(ml/100 ml)		Muscle blood flow (ml/100 G/min)	
Control	Exercise	Control	Exercise	Control	Sepsis	Control	Sepsis
2.45	3.33	4.83	26.90	6.90	6.18	0.95	5.13
2.48	4.13	4.34	25.80	3.39	2.90	3.73	9.03
4.44	6.94	2.86	29.60	7.85	3.01	2.39	3.06
3.94	7.32	2.92	25.0	2.61	0.72	5.51	13.18
5.70	8.79	1.13	14.50	3.81	6.93	2.70	7.00
				2.96	3.17	5.68	14.68
				4.19	4.95	4.27	8.79
				5.70	6.89	1.13	6.35
				3.94	1.95	2.92	13.4

TABLE IV

SUMMARY OF CHANGES IN MUSCLE BLOOD FLOW AND ARTERIOVENOUS OXYGEN DIFFERENCE IN SEPSIS AND AFTER EXERCISE

MEAN VALUES

	EXERCISE			SEPSIS		
	Control	Exercise	% change	Control	Sepsis	% change
Femoral A-V O_2 difference (ml/100 ml)	3.80	6.10	+60%	4.60	4.08	-11%
Muscle blood flow (ml/100 G/min)	3.21	24.4	+660%	3.25	8.96	+176%

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